REMARKS

Entry of the foregoing amendment for purposes of appeal is respectfully requested. The amendment cancels claims and places the application in better form for an appeal should an appeal become necessary.

Entry of the foregoing amendment, and further favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

As correctly indicated in the Office Action Summary, claims 143-164 are pending in the application and are under consideration; claims 143-164 stand rejected.

By way of the instant Amendment, claims 143-147, 159 and 162 have been canceled without prejudice or disclaimer to the subject matter disclosed therein. Applicants reserve the right to file a continuation or divisional application directed to the canceled subject matter.

Claim rejection under 35 U.S.C. § 102(e):

Claims 143-147, 159 and 162 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Nair et al. (U.S. Patent Number 5,831,068). Without agreeing to any allegation of the rejection, but simply in order to reduce the number of issues on appeal, claims 143-147, 159 and 162 have been canceled. Consequently, the rejection is moot.

Claim rejection under 35 U.S.C. § 102(b):

Claims 155-157, 160 and 161 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Hammond et al. (Nature, 364:158-161, 1993). Applicants maintain that the rejection has been traversed.

Tumor metastasis frequently relies on impaired MHC presentation to permit the tumor cells to avoid recognition and attack by the immune system. The novel methods of the present invention are directed to a process for isolating immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation, and cells that induce such selective recognition in activate CD8+ T lymphocytes. Prior to the discovery by the present inventors, it was not known or even believed that it would be possible to induce immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation.

The process of Claim 155 comprises (a) stimulating isolated immunological effector cells in vitro with cells isolated according to the method of claim148; and (b) isolating immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation. In the method of claim 148, cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation have been isolated after treating cells in vitro with an effective dose of a substance that impairs cellular peptide processing for MHC presentation.

Thus, the method of the present invention results in the isolation of immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation. Hammond et al. does not teach a method that accomplishes this goal. The CTL that Hammond uses in their method are specific for HIV epitopes.

By contrast, Hammond et al. expressed *env* and gp120 from HIV in T2 cells, which have a TAP-1 and Tap-2 knockout deletion. Hammond et al. found that is was possible for CD8+ CTL specific for the HIV protein epitopes to lyse T2 cells expressing gp120 even in a TAP defective background.

However, Hammond et al. did not treat cells in vitro with an effective dose of a substance that impairs cellular peptide processing for MHC presentation or isolate cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as required by the methods of claim 148 and claim 155.

Not having isolated any cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation Hammond et al. did not teach or suggest combining such cells, or antigens, or epitopes expressed by such cells with a pharmaceutically acceptable additive as required by claim 160.

Furthermore, Hammond et al. did not stimulate immunological effector cells in vitro with cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as required by the method of claims 155-157.

Therefore, Hammond et al. did not perform, teach, or even suggest a method as recited in claims 155-157.

Not having isolated any isolating immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation, Hammond et al. could not teach or suggest a composition comprising such cells as required by claim 161.

Hammond et al. did not anticipate the present invention, and the rejection should be withdrawn.

Claim rejection under 35 U.S.C. § 103(a):

Claims 148-158, 160 and 161 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Nair et al., (U.S. Patent Number 5,831,068), in view of Sandberg et al. (Eur Journal of Immunology, 26:288-93, 1996) and Skipper et al. (J. Experimental Medicine, 183:527-34, 1996). Applicants maintain that the rejection has been traversed.

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

Nair et al. is directed to a method of short-circuiting the MHC class I presentation pathway and inserting exogenous peptides in place of the peptides that would otherwise be presented. The purpose of Nair et al. is to provide an efficient means to prepare cells that present an **exogenous** epitope of interest. Nair et al. is not concerned with and did not teach or suggest isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation.

Nair et al. teaches treating cells with a substance that impairs cellular peptide processing for MHC presentation. However, Nair et al. does not teach or even suggest isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation as required by claim 148. Nair et al. isolates only cells that present **exogenous** epitopes.

Nair et al. did not appreciate and did not suggest that it would be possible to isolate cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC and doing so would be contrary to the purpose of Nair et al.

Sandberg et al. studies the CD8+ CTL population in TAP1 (-/-) mice. Sandberg et al. found that TAP1 defective mice possessed a range of peptide specific CD8+ CTL. Sandberg et al. did not teach or suggest treating cells with a substance that impairs cellular peptide processing for MHC presentation. Sandberg et al. did not teach or even suggest isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as required by claim 148. For example, Sandberg et al. did not show that the CD8+ CTL of TAP1 defective mice was selective for cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation and did not suggest isolating such cells.

Skipper et al. bears almost no discernable relationship to the presently claimed invention or to Sandberg et al. or to Nair et al. The Office alleges that Skipper et al. teaches that post translation modification can lead to generation of new antigens which are relevant to tumor rejection. It is not clear how this would suggest any of the steps of the presently claimed methods. Skipper et al. did not teach or suggest treating cells with a substance that impairs cellular peptide processing for MHC presentation. Skipper et al. did not teach or even suggest isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as required by claim 148. Skipper et al. clearly fails to cure the deficiencies of Nair et al. and Sanderg et al.

Therefore, the combination of Nair et al., Sandebrg et al., and Skipper et al. fails to even suggest all the steps of claim 148.

Furthermore, there could not have been any motivation to modify Nair et al. as the Office has proposed, because the proposed modification would have been contrary to the purpose of the teaching of Nair. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Nair is directed to a method of preparing cells presenting **exogenous**

epitopes of choice, the very idea of isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation would have been contrary to the object of the method of Nair et al.

Moreover, the combination of Nair et al. with Sandberg et al. and Skipper et al. does not suggest the insight necessary to provide a reasonable expectation of success in modifying Nair to arrive at the present invention. In particular, the combination of references does not suggest that is would have been possible to isolate cells that are **capable of inducing a CTL response that is specific for endogenous epitopes associated with impaired cellular peptide processing for MHC presentation**. The finding Sandberg et al. that TAP1 (-/-) mice possesses a diverse CTL response and the hypothesis of Skipper et al. that post translation modification can lead to generation of new antigens which are relevant to tumor rejection do not suggest that it would be possible to isolate cells that would induce a **specific** CTL response to the endogenous epitopes of cells with impaired cellular peptide processing for MHC presentation.

Thus, none of the requirements of a prima facie case of obviousness have been satisfied by the prior art in this rejection. The rejection should be withdrawn.

Claim rejections under 35 USC § 112:

Claims 155-157, 160, 161 and 164 have been rejected under 35 U.S.C. § 112 for allegedly failing to comply with the written description requirement. Applicants maintain that the rejection has been traversed.

The Office has previously asserted that the methods of claims 155-157 rely upon the cells isolated according to the method of claim 148. The Office has alleged that the cells that are isolated by the method of claim148 are not adequately described. In making this rejection, the Office implies that no process of manufacture can ever be sufficiently described if the process comprises the production of a novel intermediate material that is defined by its method of manufacture. This cannot be so. The Office has cited no authority that supports such a proposition.

The Office now asserts that the cells isolated in claim 148 rely upon treatment with a "substance" that is not adequately described. The Office alleges that claim 148 is a method of screening for the "substance." This is simply incorrect. Moreover, it is noted that the

Office has acknowledged that the method of claim 148 (including all the elements thereof) is adequately described, as claim 148 has not been included in the present rejection.

The Office has not adduced any basis to doubt that one or ordinary skill in the art would know and recognize a substance characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC class I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7-1 as recited in claim 148. A wide variety of representative examples of such substances are described in the specification at page 8. Therefore, the Office is simply wrong to assert that method of claim 148 amounts to a method of screening for the "substance." Claim 148 recites a process that utilizes a substance that is characterized by its function. The principles underlying the recited function and a representative number of examples of substances possessing the recited function are described in the specification so that a person of ordinary skill in the art would recognize that the inventors were in possession of the method of claim 148.

Claim 148 defines a process of manufacture. The cells isolated by the method of claim 148 have distinctive properties that are described in claim 148 by their selective induction of a specific immune response. The Office has not adduced any basis to doubt that the steps of claim 148 can produce isolated cells having the properties recited in claims 148. Such a claim is analogous to claims to antibodies, including those yet to be isolated, which are held to be adequately described if the corresponding antigen is fully described. *See, Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir 2004). Antibodies are described by functional properties, which are a result of the process by which they are made. Here, the cells isolated by the method of claim 148 are described both in terms of the method of making the cells and by the ability of the cells to induce a specific response from immune effector cells.

Claim 155 is directed to an extension of the method of claim 148 which takes the product of claim 148 as an intermediate material and produces other isolated cells. Claim 157 is a product-by-process claim directed to a composition comprising such cells. Claim 155 and the claims that depend from claim 155 simply utilize the product of the method of claim 148 in further processing steps that result in a further related product that is, itself, defined by the process used to make it. Claim 161 is directed to a composition comprising the product of claim 155.

Product by process claims are proper under 35 U.S.C. § 112. *See, e.g.,* M.P.E.P. § 2173.05(p); *see also, In re Luck*, 476 F.2d 650, 177 USPQ 523 (CCPA 1973); *In re Pilkington*, 411 F.2d 1345, 162 USPQ 145 (CCPA 1969); *In re Steppan*, 394 F.2d 1013, 156 USPQ 143 (CCPA 1967). It is long established that a product may be adequately described as required under 35 U.S.C. § 112, by the method in which it is made. Method claims that recite the use of such products can be no less adequately described than method claims that take one material and make another.

Working examples of claims 155-157, 160 and 161, as well as the related claim 148 are provided by Example 4 in the specification. B6 spleen cells were stimulated with TAP-/- and RMA-S.B7-1 cells. TAP was directly ablated by knocking out gene expression in two independent ways. This stimulation of B6 cells reproducibly resulted in cytotoxic responses against RMA-S and TAP -/- targets. The example demonstrates that the response is sepcific to the novel endogenous self-antigen changes being expressed on the cells that have their TAP function altered. The reproducibility of the stimulation described in the example demonstrates that the claimed methods predictably produce cells having the recited properties.

Therefore, the Office's alleged basis for the rejection is not supported by fact or law, and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

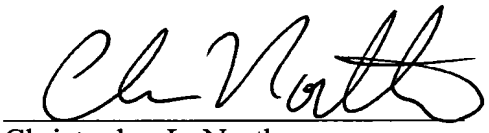
In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: November 1, 2006

By: 

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